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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/644,289	05/10/96	KULESZ-MARTIN M	RPP:135D-US

18M1/0328

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EXAMINER	
EYLER, Y	
ART UNIT	PAPER NUMBER
1806	

DATE MAILED: 03/28/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/644,289	Applicant(s) Kulesz-Martin
	Examiner Yvonne Eyler	Group Art Unit 1806

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-15* is/are pending in the application.

Of the above, claim(s) *12-14* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-11 and 15* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims *1-15* are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-11 and 15, drawn to cDNA encoding alternatively spliced p53 in plasmids or viral vectors, classified in class 536, subclass 23.1.

II. Claims 12-14, drawn to an antibody which specifically binds alternatively spliced p53 protein, classified in class 530, subclass 387.7.

2. The inventions are distinct, each from the other because of the following reasons:

The inventions of Groups I and II are drawn to two entirely different products which are biochemically, structurally, and functionally different. The cDNA and the antibody cannot be used interchangeable in any methods utilizing one or the other.

3. During a telephone conversation with Michael L. Dunn on 3/5/97 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-11 and 15. Affirmation of this election must be made by applicant in responding to this Office action. Claims 12-14 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Specification

4. The disclosure is objected to because of the following informalities:

The specification discloses sequences without referring to them by Seq. ID No. The specification also refers to "the original patent application" which would have little meaning in an issued patent. Please note that incorporation by reference is proper only where the incorporated application is an allowed U.S. Patent application of a U.S. Patent.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. Claims 1-11 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite in that they only describe the compositions by an arbitrary laboratory designation, p53as. There is nothing in the claims, other that p53as, which distinctly claims the protein. Others in the field may isolate the same cDNA and give such an entirely different name. Applicant should particularly point out and distinctly claim the cDNA by including other, defining characteristics associated with the cDNA in the claim language. Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that molecule is.

Claims 2 and 7 are vague and indefinite in that the metes and bounds of "a portion" cannot be determined. It is not clear what the boundaries of "a portion" are.

Claim 15 is vague and indefinite in the recitation "at least a unique part of SLRPFKALVREKGHRPSHSC." The metes and bound of the claim cannot be determined because the boundaries of "at least a unique part" are not defined. Further, the claim refers to a sequence but does not include a Seq. ID. No. which is improper.

6. Claims 1-11 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is not enabling for the claims as broadly drawn. The claims are drawn to any alternatively spliced form of p53 which has any size portion identical to any size portion in wildtype p53. Claim 15 is further drawn to "at least a unique part of" a specified intron 10 sequence, the size of which is not defined and could be as little as one amino acid, such as phenylalanine, which is a unique part because it is only found once. (Note that the sequence in claim 15 must be referred to as a Seq. ID. No. as noted above)

The specification teaches a single alternatively spliced form of p53 which is distinguishable from wildtype p53 only in 17-50 C-terminal amino acids and a 9 amino acid truncation due to alternative splicing of intron 10, and in that it lacks the C-terminal negative regulatory domain. No other versions of alternatively spliced p53 cDNA molecules are taught. Further, other than the C-terminal regions discussed above and the 9 amino acid truncation of intron 10, no specific portions between alternatively spliced p53 and wildtype p53 art taught to be identical, different, or

unique. Similarly, the specific sequences of intron 10 or the recited sequence of intron 10 which are unique and necessary to form an alternatively spliced p53 molecule with the required characteristics of function are taught. The amino acid sequence of a protein such as p53 determines its structural and functional properties, and predictability of which amino acids can be substituted or deleted within a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of alternatively spliced forms of p53, other than the instantly disclosed molecule (for which a Seq. ID No. is needed), it is unpredictable as to which and what size amino acid regions and which amino acid changes, if any, meet the limitations of the claim. Furthermore, while recombinant techniques are available, it is not routine in the art to screen large numbers of substituted proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. Therefore, one of ordinary skill would require guidance, such as information regarding the extent of, the precise location of, and the specific amino acid changes which would result in the preservation of activity. Therefore, it would require undue experimentation by one of skill in the art to practice the invention as claimed without further guidance from the instant specification.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolf et al (IDS; Mol. Cell Biol. 5:127-132, 1985).

Wolf et al disclose a murine cDNA clone of p53 in a plasmid (pM8) representing a single mRNA molecule which gives rise to a distinct immunological p53 molecule which is recognized by some antibodies to p53, but not others, indicating that at least a portion of the clone is identical to wildtype p53. Wolf et al further teach that the variation is likely due to alternative splicing which naturally occurs (p. 127 and 130). Thus, the disclosure of Wolf et al anticipates the instant invention of claims 1-4.

9. Claims 1-4 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Han et al (IDS; Nuc.Acids Res. 20:1979-1981, 1992)

Han et al disclose a plasmid containing a murine cDNA of an alternatively spliced p53 (AS-p53) which contains an extra 96 bp from intron 10 which results in premature termination of the p53 protein product giving rise to a 9 amino acid truncation and a 25 amino acid difference at the C-terminus of the molecule. Otherwise, the molecule is identical to wildtype p53 (see the

abstract; p. 1980, column 2 last paragraph to p. 1981, column 1 first paragraph and 3rd paragraph).

10. Claims 1-4 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Arai et al (IDS; Mol. Cell Biol. 6:3232-3239, 1986).

Arai et al disclose a plasmid containing a murine cDNA clone, p53-M8, which represents a mRNA species generated by alternative splicing. The clone contains a 96 bp insert of intron 10, including the sequence of claim 15 (see figure 4) which results in a protein product which differs from wildtype by being truncated by 9 amino acids (See the abstract; p. 3233, column 1, second paragraph; p. 3234, column 2, 3rd paragraph; p. 3235, column 2; p. 3238, column 1).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 5-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolf et al (Mol. Cell Biol. 5:127-132, 1985), Han et al (Nuc.Acids Res. 20:1979-1981, 1992), or Arai et al (Mol. Cell Biol. 6:3232-3239, 1986) in view of Lee et al (IDS; EP 529160).

Wolf et al, Han et al, or Arai et al do not disclose the alternatively spliced cDNA in a viral or baculovirus vector. They each discuss the benefits of further biochemical and biological

characterization of the alternatively spliced p53. (See Han et al, p. 1981, column 2; Arai et al, p. 3238, column 2; and Wolf et al, p. 131, column 1).

Lee et al disclose a method of producing substantial quantities of a desired polypeptide by expressing cDNA clones in baculovirus vectors for culture in insect cells to produce large quantities of purified tumor suppressor gene product useful for study and therapeutics (See the abstract; p. 2, lines 40-45; p. 4, lines 10-15; and p. 5 lines 10-20).

It would have been obvious and one of ordinary skill would have been motivated to use the baculovirus vector system of Lee et al with a reasonable expectation of success as a vector for other tumor suppressor proteins such as the alternatively spliced p53 cDNA of Wolf et al, Han et al and Arai et al to allow the further biochemical and biological characterization of the alternatively spliced p53.

NO CLAIM IS ALLOWED.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvonne Eyler, Ph.D. whose telephone number is (703) 308-6564 and FAX number is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

LILA FEISEE
SUPERVISORY PATENT EXAMINER
GROUP 1800

Yvonne Eyler, Ph.D.
March 26, 1997